Pulmonary complications of pneumococcal community-acquired pneumonia: incidence, predictors, and outcomes

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Abstract

The aim of this study was to evaluate the clinical characteristics, predictors and outcomes of pneumococcal pneumonia developing pulmonary complications and the distribution of pneumococcal serotypes. It was a prospective study including all adult patients admitted to the Hospital Clinic of Barcelona, Spain (2001–2009) with the diagnosis of pneumococcal pneumonia. Microbiological investigation was systematically performed, including antimicrobial susceptibility and serotype distribution (only invasive strains isolated during 2006–2009). Complicated pneumonia was defined as the presence of one or more pulmonary complications: pleural effusion, empyema, or multilobar infiltrates. We included 626 patients, and 235 (38%) had the following pulmonary complications: pleural effusion, 122 (52%); empyema, 18 (8%); and multilobar infiltration, 151 (64%). Forty-six (20%) patients had more than one complication. Patients with pulmonary complications showed a higher rate of intensive-care unit admission (34% vs. 13%, p <0.001), a higher rate of shock (16% vs. 7%, p <0.001), a longer length of stay (9 days vs. 6 days, p <0.001), and a lower rate of penicillin resistance (14% vs. 25%, p 0.013), but similar mortality (9% vs. 8%). No significant differences were observed in the serotype distribution between complicated and uncomplicated pneumonia. Chronic obstructive pulmonary disease (COPD) (OR 0.38, 95% CI 0.23–0.63; p <0.001) was a protective factor against pulmonary complications, whereas chronic liver disease (OR 3.60, 95% CI 1.71–7.60; p 0.001), admission C-reactive protein level ≥18 mg/dL (OR 2.77, 95% CI 1.91–4.00; p <0.001) and admission creatinine level >1.5 mg/dL (OR 2.01, 95% CI 1.31–3.08; p 0.001) were risk factors for pulmonary complications. Complicated pneumonia was characterized by a more severe clinical presentation, but was not associated with increased mortality. Resistance to antibiotics was lower in complicated cases. No significant differences were observed in the serotype distribution between complicated and uncomplicated pneumonia. In the multivariate analysis, COPD was a protective factor against pulmonary complications.

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Introduction

Streptococcus pneumoniae is the most frequent aetiological agent of community-acquired pneumonia (CAP) [1]. Since the addition of a heptavalent protein–polysaccharide conjugate vaccine (PCV7) to the routine childhood vaccination schedule, numerous studies have documented declining rates of colonization with PCV7 serotypes and a lower incidence of PCV7-type invasive pneumococcal disease (IPD) among young children and adults. Despite the effectiveness of the conjugate vaccine, the emergence of IPD caused by non-vaccine serotypes has been reported [2–4].

Most cases of adult pneumococcal pneumonia are self-limiting, and patients fully recover. A subset of patients have a more complicated course associated with pulmonary compli-

cations, including pleural effusion, empyema, and multilobar consolidation or cavitations.

Among potential complications, pleural effusion is very frequent, as up to 57% of hospitalized pneumonia patients may develop it [5,6]. Moreover, it is considered to be an indicator of severity of pneumonia, and is clearly associated with an increased risk of treatment failure [7–9].

The occurrence of empyema is one of the main factors associated with poor outcome in CAP [10], and is a frequent cause of prolonged treatment (medical and surgical) and hospital stay [11], and even of treatment failure [7,8].

Multilobar consolidation is one of the minor criteria for defining severe CAP and evaluating the need for intensive-care unit (ICU) admission, and is associated with treatment failure [7,8,10]. Moreover, different authors have found that multilobar infiltration is an independent risk factor for increased mortality in CAP [9,12]. Adults with these complications often require prolonged hospitalization, and are at risk of significant and long-lasting morbidity [5,9].

Although the overall burden of IPD has decreased, the incidence of complicated pneumonia may be rising. Several studies have shown an increase in the frequency of pulmonary complications among children [13–15]. This increase does not appear to be related to the concurrent increase in the frequency of penicillin-resistant *S. pneumoniae*, but does appear to be related to the introduction of virulent clones expressing non-vaccine serotypes, especially serotype 1. Serotype distributions may be relevant in this trend. Likewise, host factors such as age, gender and the presence of comorbidities have been related to invasive pneumococcal pneumonia and may be risk factors for the development of complicated pneumonia. On the other hand, data on the clinical manifestations in an adult population with complicated pneumococcal pneumonia are limited. This study was undertaken to evaluate the clinical characteristics and outcomes of adults with pneumococcal pneumonia, especially those with pulmonary complications.

Materials and Methods

Study population

The study population consisted of adults consecutively admitted to the Hospital Clinic of Barcelona (Spain), an 800-bed third-level hospital covering an urban population of 540 000 inhabitants, between 2001 and 2009, with a diagnosis of pneumococcal pneumonia.

At the initial visit, patients underwent a complete clinical history and physical examination. Patients were stratified into risk classes with the validated prediction rule calculated according to Pneumonia Severity Index (PSI) scores. Empirical antibiotic treatment was administered according to hospital guidelines. All surviving patients were visited at 30–40 days after discharge.

Microbiological evaluation and diagnostic criteria

Regular sampling included sputum specimens, two blood cultures and urine samples for detection of *S. pneumoniae* (Binax Now *S. pneumoniae* Urinary Antigen Test; Emergo Europe, The Hague, The Netherlands) and *Legionella pneumophila* serogroup 1 (Binax Now *L. pneumophila* Urinary Antigen Test; Trinity Biotech, Bray, Ireland). Samples from pleural fluid puncture, tracheobronchial aspiration and blind bronchoalveolar lavage were obtained according to the judgement of the attending physician.

The diagnosis of pneumonia was established in the presence of clinical symptoms and a new infiltrate on the chest radiograph and no alternative diagnosis during follow-up. The aetiology of pneumococcal pneumonia was determined in cases with a positive valid sputum culture, positive blood culture, positive pleural fluid and transthoracic needle aspiration cultures, positive urinary antigen for *S. pneumoniae*, bacterial growth in cultures of tracheobronchial aspiration specimens of $\geq 10^5$ CFU/mL, bacterial growth in cultures of phosphate-buffered saline of ≥10 CFU/mL, and bacterial growth in cultures of bronchoalveolar lavage specimens of $\geq 10^4$ CFU/mL.

Pneumococcal isolates were identified with standard microbiological methods. All strains isolated from normally sterile sites were routinely frozen at −70°C in skimmed milk. Later, molecular serotype detection was performed with a published Multiplex real-time assay [9] at the Molecular Microbiology Department, Hospital Sant Joan de Deu, Barcelona. This PCR procedure allows differentiation of 24 serotypes (1, 3, 5, 4, 6A, 6B, 7F/A, 8, 9V/A/N/L, 14, 15B/C, 18C/B, 19A, 19F/B/C, 23F and 23A). Strains not typeable by real-time PCR were consecutively serotyped with the Quellung reaction, using rabbit polyclonal antisera from the Statens Serum Institute (Copenhagen, Denmark) at the National Pneumococcus Reference Centre (Majadahonda, Madrid). Serotyping was performed only in invasive strains isolated during the period from 2006 to 2009.

Strains were initially screened for susceptibility to antimicrobial agents with Sensititre (Trek Diagnostic Systems, East Grinstead, UK). Penicillin susceptibility and other antibiotic susceptibilities were defined according to the 2008 breakpoints of the CLSI [16].

Definitions of pulmonary complications

Complicated pneumonia was defined as the presence of one or more of the following pulmonary complications: pleural effusion, empyema, or multilobar infiltrates. We included only meaningful pleural effusions in which thoracocentesis

was performed and pleural fluid was obtained. Pleural empyema was diagnosed if (i) the Gram stain was positive or a pathogen was cultured from pleural fluid, or (ii) at least two of the following criteria were fulfilled by pleural fluid analysis: glucose ≤40 mg/dL, lactate dehydrogenase ≥1000 u/L, pH ≤7.2, and white blood cell count of 10 000 cells/mL. Multilobar pneumonia was defined as a chest X-ray infiltrate involving two or more lobes [2].

Exclusion criteria were as follows: (i) severe immunosuppression, such as solid organ or bone marrow transplantation or AIDS, receiving chemotherapy or other immunosuppressive drugs (>20 mg of prednisone equivalent per day for 2 weeks or more), or asplenia; (ii) hospitalization in the preceding 21 days; (iii) active tuberculosis; and (iv) healthcare-associated pneumonia according to American Thoracic Society/Infectious Diseases Society of America guidelines [7]. Patients were categorized into two groups on the basis of the presence or absence of pulmonary complications: uncomplicated and complicated pneumonia.

Statistical analysis

Categorical variables were described by frequencies and percentages, and continuous variables by means and standard deviations, or the median and interquartile range for data that were not normally distributed (Kolmogorov–Smirnov test). Categorical variables were compared by use of the chi-square test or Fisher's exact test where appropriate. Continuous variables were compared by use of Student's *t*-test once normality was demonstrated; otherwise, the non-parametric Mann–Whitney *U*-test was performed.

Univariate and multivariate logistic regression analyses were performed to identify variables predictive of patients with pulmonary complications (dependent variable). The variables analysed univariately were: age, gender, smoking, alcohol consumption, previous antibiotic use, influenza vaccine, pneumococcal vaccine, systemic corticosteroids, chronic obstructive pulmonary disease (COPD), chronic cardiovascular disease, diabetes mellitus, neurological disease, chronic renal failure, chronic liver disease, bacteraemia, creatinine, C-reactive protein (CRP) level, and white blood cell count. Interactions between variables were specifically searched for. Variables that showed a significant result univariately ($p < 0.1$) were included in the multivariate logistic regression backward stepwise model. Variables that were highly correlated were excluded from multivariate analyses. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the model [17]. All tests were two-tailed, and significance was set at 5%. All analyses were performed with SPSS version 16.0 for Windows (SPSS, Chicago, IL, USA).

Results

General characteristics of the study population

A total of 626 patients were included during the study period from 2001 to 2009. The mean age was 63.6 ± 18.9 years (289 patients (46%) were aged ≤65 years), and 355 (57%) of the patients were male.

On admission, the patients were classified by PSI score as being in the low-risk group (I–III) (*n* = 299, 48%), the intermediate-risk group (IV) (*n* = 214, 34%), and the high-risk group (V) (*n* = 113, 18%). Fifty-four patients (9%) died within 30 days of admission. Table 1 summarizes the main characteristics of the 626 patients.

Pulmonary complications

Of the 626 patients, 235 (38%) had pulmonary complications, distributed as follows: pleural effusion, 122 (52%); empyema, 18 (8%); and multilobar infiltration, 151 (62%). Forty-six (20%) had more than one of the pulmonary complications. The characteristics of the patients with complicated and uncomplicated pneumonia are summarized in Tables 2–5.

TABLE 1. Demographic and clinical characteristics of patients with pneumococcal pneumonia

General characteristics	Pneumococcal pneumonia (*N* = 626)
Demographics	
Age (years), mean (SD)	63.6 (18.9)
Sex (male), *n* (%)	355 (57)
Current smoking, *n* (%)	198 (31.9)
Current alcohol abuse, *n* (%)	104 (16.8)
Previous antibiotic, *n* (%)	85 (16.0)
Influenza vaccine, *n* (%)	213 (39.1)
Pneumococcal vaccine, *n* (%)	79 (14.6)
Inhaled corticosteroid, *n* (%)[a]	133 (21.3)
Systemic corticosteroid, *n* (%)[a]	13 (2.2)
Comorbidity, *n* (%)	
Chronic respiratory disease	275 (44.2)
Bronchiectasis	64 (10.3)
COPD	130 (21.0)
Asthma	41 (6.6)
Other	40 (6.4)
Chronic cardiovascular disease, *n* (%)	84 (13.5)
Diabetes mellitus, *n* (%)	105 (16.9)
Neurological disease, *n* (%)	87 (14.0)
Chronic renal failure, *n* (%)	31 (5.0)
Chronic liver disease, *n* (%)	38 (6.1)
Pulmonary complications, *n* (%)[b]	
Multilobar infiltration	151 (64.2)
Pleural effusion	122 (51.9)
Empyema	18 (7.6)
PSI I–III, *n* (%)	299 (47.8)
PSI IV–V, *n* (%)	327 (52.2)
Bacteraemia, *n* (%)	206 (32.9)
ICU admission, *n* (%)	132 (21.1)
Mechanical ventilation, *n* (%)	55 (9.8)
Length of hospital stay (days), median (IQR)	9.4 ± 6
30-day mortality, *n* (%)	54 (8.7)

COPD, chronic obstructive pulmonary disease; ICU, intensive-care unit; IQR, interquartile range; PSI, Pneumonia Severity Index; SD, standard deviation.
[a]Treatment before admission for pneumonia episode.
[b]Forty-six patients had more than one pulmonary complication.

TABLE 2. Characteristics of patients with complicated community-acquired pneumonia (CAP) and uncomplicated CAP

Variable	Complicated CAP (*N* = 235)[a]	Uncomplicated CAP (*N* = 391)[a]	p-Value
Demographics			
Age (years), mean (SD)	61.6 (18.5)	64.9 (19.0)	0.027
Age >65 years, *n* (%)	111 (47.2)	226 (57.8)	0.010
Sex (male), *n* (%)	129 (54.9)	226 (57.8)	0.48
Current smoking, *n* (%)	83 (35.8)	115 (29.6)	0.11
Current alcohol abuse, *n* (%)	47 (20.2)	57 (14.8)	0.07
Previous antibiotic, *n* (%)	34 (17.4)	51 (15.0)	0.47
Influenza vaccine, *n* (%)	64 (31.4)	149 (43.7)	0.004
Pneumococcal vaccine, *n* (%)	23 (11.3)	56 (16.5)	0.10
Inhaled corticosteroid, *n* (%)[b]	29 (12.4)	104 (26.7)	<0.001
Systemic corticosteroid, *n* (%)[b]	3 (1.4)	10 (2.7)	0.30
Comorbidity, *n* (%)			
Chronic respiratory disease			<0.001
Bronchiectasis	26 (11.2)	38 (9.8)	0.58
COPD	28 (12.0)	102 (26.2)	<0.001
Asthma	19 (8.2)	22 (5.7)	0.22
Other	28 (7.2)	12 (5.2)	0.31
Chronic cardiovascular disease, *n* (%)	25 (10.7)	59 (15.1)	0.12
Diabetes mellitus, *n* (%)	34 (14.7)	71 (18.3)	0.25
Neurological disease, *n* (%)	33 (14.1)	54 (14.0)	0.97
Chronic renal failure, *n* (%)	9 (3.9)	22 (5.7)	0.32
Chronic liver disease, *n* (%)	22 (9.4)	16 (4.1)	0.008
Clinical manifestations, *n* (%)			
Fever	215 (91.9)	336 (85.9)	0.026
Dyspnoea	191 (81.3)	267 (68.3)	<0.001
Chest pain	146 (62.1)	215 (55.1)	0.09
Acute renal failure	54 (23.4)	41 (10.6)	<0.001
Shock	37 (15.9)	28 (7.2)	<0.001
Clinical findings			
Temperature (°C), median (IQR)	37.6 (1.6)	38.0 (1.5)	0.013
Systolic blood pressure (mmHg), median (IQR)	120.0 (39.0)	124.5 (34.5)	0.08
Laboratory findings			
Creatinine (mg/dL), median (IQR)	1.1 (0.8)	1.1 (0.5)	0.11
Creatinine >1.5 mg/dL, *n* (%)	62 (26.4)	62 (15.9)	0.001
C-reactive protein level (mg/dL), median (IQR)	25.1 (18.3)	17.4 (19.4)	<0.001
C-reactive protein level ≥18 mg/dL, *n* (%)	166 (71.6)	182 (48.0)	<0.001
WBC count (10^9 cell/L), median (IQR)	14.9 (10.3)	15.9 (9.0)	0.028
Saturated O_2 (%), median (IQR)	92.0 (6.9)	93.9 (5.5)	<0.001
Saturated O_2 <92%, *n* (%)	81 (46.8)	84 (32.7)	0.003
P_aO_2/F_iO_2 ratio, median (IQR)	266.7 (71.4)	287.1 (89.9)	<0.001
P_aO_2/F_iO_2 ratio <200, *n* (%)	28 (14.5)	17 (5.4)	<0.001
PSI IV–V, *n* (%)	134 (57.0)	193 (49.4)	0.06
Bacteraemia, *n* (%)	93 (39.6)	113 (28.9)	0.006
ICU admission, *n* (%)	80 (34.0)	52 (13.3)	<0.001
Mechanical ventilation, *n* (%)	32 (15.5)	23 (6.5)	<0.001
Length of hospital stay (days), median (IQR)	9.0 (9.0)	6.0 (6.0)	<0.001
30-day mortality, *n* (%)	22 (9.4)	32 (8.2)	0.62

COPD, chronic obstructive pumonary disease; ICU, intensive-care unit; IQR, interquartile range; PSI, Pneumonia Severity Index; SD, standard deviation; WBC, white blood cell.
[a]Complicated CAP caused by multilobar involvement (two or more lobes) in 151 cases (64%), pleural effusion in 122 cases (52%), and empyema in 18 cases (8%). Forty-six (20%) patients had more than one complication.
[b]Treatment before admission for pneumonia episode.

TABLE 3. Patients with multilobar involvement

Variable	Multilobar involvement (*N* = 155)
PSI IV–V, *n* (%)	89 (58.9)
Bacteraemia, *n* (%)	65 (43.0)
ICU admission, *n* (%)	57 (37.7)
Mechanical ventilation, *n* (%)	28 (21.5)
Length of hospital stay (days), median (IQR)	9.0 (9.0)
30-day mortality, *n* (%)	18 (11.9)

ICU, intensive-care unit; IQR, interquartile range; PSI, Pneumonia Severity Index.

TABLE 4. Patients with pleural effusion

Variable	Pleural effusion (*N* = 122)
PSI IV–V, *n* (%)	72 (59.0)
Bacteraemia, *n* (%)	40 (32.8)
ICU admission, *n* (%)	44 (36.1)
Mechanical ventilation, *n* (%)	13 (12.0)
Length of hospital stay (days), median (IQR)	10.0 (9.0)
30-day mortality, *n* (%)	10 (8.2)

ICU, intensive-care unit; IQR, interquartile range; PSI, Pneumonia Severity Index.

The main parameters of clinical severity (PSI, ICU, mechanical ventilation (MV), etc.) showed a homogeneous distribution among patients with different pulmonary complications, with the exception of bacteraemia, which showed a tendency to be more frequent among patients with multilobar involvement (Tables 2–5). A higher proportion of patients aged >65 years was observed in the complicated pneumonia group (47% vs. 58%, p 0.010). There were no differences in smoking or alcohol consumption between the two groups. There was a difference in temperature at admission

TABLE 5. Patients with empyema

Variable	Empyema (*N* = 18)
PSI IV–V, *n* (%)	10 (55.6)
Bacteraemia, *n* (%)	4 (22.2)
ICU admission, *n* (%)	7 (38.9)
Mechanical ventilation, *n* (%)	2 (14.3)
Length of hospital stay (days), median (IQR)	13.5 (9.0)
30-day mortality, *n* (%)	2 (11.1)

ICU, intensive-care unit; IQR, interquartile range; PSI, Pneumonia Severity Index.

(p 0.013). CRP level ≥18 mg/dL (p <0.001) and creatinine level >1.5 mg/dL (p 0.001) were higher in patients with complicated pneumonia. However, patients with complicated pneumonia had fewer comorbidities (<1 comorbidity) than patients with uncomplicated pneumonia (57% vs. 69%, p 0.003), and a lower rate of influenza vaccination (p 0.004).

Complicated pneumonia patients had a longer length of hospital stay (p <0.001), more frequent admission to the ICU (p <0.001), more frequent shock (p <0.001) and longer time to clinical stability (8 days vs. 5 days, p <0.001) than uncomplicated pneumonia patients. The mortality rate was similar in both groups (9% vs. 8%), despite the higher frequency of bacteraemia and shock observed in complicated cases (p 0.005 and p 0.001, respectively). The analysis of mortality did not show significant differences between groups when sthe different pulmonary complications were split (multilobar, 18 (12%); pleural effusion, 10 (8%); and empyema, 2 (11%)) (Tables 2–5).

Diagnosis of pneumococcal pneumonia resistance to antibiotics and serotypes

The *S. pneumoniae* antigen was detected in 404 patients from urine (65%), and was isolated by culture in 221 (35%) sterile samples (203 from blood and 18 from pleural fluid). In addition, *S. pneumoniae* was isolated in 13 (2%) patients from bronchial aspirate sample and in 128 (20%) from sputum samples.

MIC testing was performed for 333 of 362 (92%) *S. pneumoniae* isolates. A total of 69 pneumococcal isolates showed some degree of penicillin non-sensitivity; resistance was intermediate (MIC 4 mg/L) in 38 and high (MIC ≥8 mg/L) in 31. In addition, 56 pneumococcal isolates were non-susceptible to erythromycin (resistance was intermediate (MIC 0.5 mg/L) in two and high (MIC ≥1 mg/L) in 54). The rates of penicillin and erythromycin resistance were almost two-fold higher in uncomplicated pneumonia cases (p 0.036 and, p 0.027, respectively) (Table 6).

Eighty-four of 221 (38%) invasive isolates were available for serotyping (2006–2009 period). The most frequent serotypes in this population were 1 (*n* = 27, 32%), 19A (*n* = 15, 18%), 3 (*n* = 7, 8%), 14 (*n* = 5, 6%), 7F (*n* = 5, 6%), and 5 (*n* = 4, 5%), as summarized in Table 7. No significant differences were observed in the serotype distribution of complicated and uncomplicated pneumonia. However, a non-significant trend for a higher frequency of serotype 19A was observed in complicated pneumonia patients. Serotypes covered by the PCV7 vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F) represented only 13% of all serotypes; 87% were not included in the vaccine. There were no statistically significant differences (p 0.42) when different serotypes and pulmonary complications were compared (PCV7 serotype vs. non-PCV7 serotypes).

Predictors of complicated pneumonia

Univariate analysis revealed the following protective factors against complicated pneumonia: age >65 years, presence of COPD, absence of chronic liver disease, absence of bacteraemia, low CRP levels (<18 mg/dL), and low creatinine levels (≤1.5 mg/dL) (Table 8).

In multivariate analysis, a protective association of complicated pneumonia was evident in patients with COPD (OR 0.38, 95% CI 0.23–0.63; p <0.001). Chronic liver disease (OR 3.60, 95% CI 1.71–7.60; p 0.001), CRP level ≥18 mg/dL

TABLE 6. Results of penicillin and erythromycin resistance testing of *Streptococcus pneumoniae* isolates from patients with complicated or uncomplicated pneumococcal pneumonia

	Complicated (*N* = 135)	Uncomplicated (*N* = 198)	p-Value
Penicillin resistance (MIC; mg/mL)[a]	No. of isolates (%)	No. of isolates (%)	0.036
Susceptible, MIC ≤2	116 (85.9)	148 (74.7)	0.013
Intermediately susceptible, MIC 4	9 (6.7)	29 (14.6)	0.024
Resistant, MIC ≥8	10 (7.4)	21 (10.6)	0.32
	Complicated (*N* = 134)	**Uncomplicated (*N* = 194)**	**p-Value**
Erythromycin resistance (MIC; mg/mL)[b]	No. of isolates (%)	No. of isolates (%)	0.027
Susceptible, MIC ≤0.25	117 (87.3)	155 (79.9)	0.08
Intermediately susceptible, MIC 0.5	2 (1.5)	0 (0)	0.17
Resistant, MIC ≥1	15 (11.2)	39 (20.1)	0.033

[a]For penicillin resistance, data were available for 333 patients.
[b]For erythromycin resistance, data were available for 328 patients.

TABLE 7. Serotype distribution of 84 *Streptococcus pneumoniae* isolates (years 2006–2009)

Pneumococcal "serotype	Complicated CAP (*N* = 52), *n* (%)	Uncomplicated (*N* = 32), *n* (%)
1	17 (32.6)	10 (31.2)
3	5 (9.6)	2 (6.2)
4	2 (3.8)	1 (3.1)
5	3 (5.7)	1 (3.1)
6A	1 (1.9)	0 (0)
7F	1 (1.9)	4 (12.5)
8	0 (0)	1 (3.1)
9N	0 (0)	1 (3.1)
9A	1 (1.9)	0 (0)
9V	2 (3.8)	0 (0)
10A	1 (1.9)	0 (0)
11F	0 (0)	1 (0)
12F	3 (5.7)	0 (0)
14	4 (7.6)	1 (3.1)
19A	11 (21.1)	4 (12.5)
19F	0 (0)	1 (3.1)
22F	0 (0)	1 (3.1)
24F	0 (0)	3 (9.3)
29	0 (0)	1 (3.1)
31	1 (1.9)	0 (0)

CAP, community-acquired pneumonia.

(OR 2.77, 95% CI 1.91–4.00; p <0.001) and creatinine level >1.5 mg/dL (OR 2.01, 95% CI 1.31–3.08; p 0.001) were risk factors for pulmonary complications (Table 8).

Antibiotic treatment

Data on antibiotic treatment was available for 620 (99%) patients, as follows: β-lactam plus macrolide (241, 39%); β-lactam plus fluoroquinolone (168, 27%); fluoroquinolone alone (136, 22%); β-lactam alone (52, 8%); macrolide plus fluoroquinolone (six, 1%); macrolide alone (two, 0.3%); and other combinations (15, 2%) (Table 9).

A β-lactam plus a fluoroquinolone was more frequently (p <0.001) administered to patients with pulmonary complications. However, a fluroquinolone as monotherapy was less frequently administered (p <0.001) (Table 9). We did not find initially inadequate antibiotic treatments in the population for which an antibiogram was available.

TABLE 9. Initial antibiotic treatment by study group

Antibiotic treatment	Complicated CAP (*N* = 235), *n* (%)	Uncomplicated CAP (*N* = 391), *n* (%)	p-Value
β-Lactam + macrolide	90 (38.3)	151 (38.6)	0.94
β-Lactam + fluoroquinolone	85 (36.2)	83 (21.2)	<0.001
Macrolide + fluoroquinolone	1 (0.4)	5 (1.3)	0.42
Other combinations	4 (1.7)	11 (2.8)	0.38
Fluoroquinolone monotherapy	32 (13.6)	104 (26.6)	<0.001
β-Lactam monotherapy	22 (9.4)	30 (7.7)	0.46
Macrolide monotherapy	0 (0)	2 (0.5)	0.53
Unknown therapy	1 (0.4)	5 (1.3)	0.42

β-Lactams include: ceftriaxone (1 or 2 g per day for 7 days); amoxycillin–clavulanic (1 g every 8 h for 7 days); cefotaxime (1 or 2 g every 8 h for 7 days). Fluoroquinolones include: levofloxacin (500 mg every 12 h or 500 mg every 24 h for 7–10 days); moxifloxacin (400 mg every 24 h for 5–7 days). Macrolides include: azithromycin (500 mg per day for 3–6 days). Other combinations include: ceftriaxone (1 g every 24 h) plus clindamicin (600 mg every 8 h); amikacin (15 mg/kg every 24 h) plus levofloxacin (500 mg every 24 h); and meropenem (1 g every 6–8 h) plus levofloxacin (500 mg every 24 h).

Discussion

The most important findings of our study are as follows: (i) pulmonary complications were frequent (38%) in patients with pneumococcal CAP; (ii) although mortality was similar between the groups, patients with pulmonary complications presented a higher rate of bacteraemia, shock, and need for MV, with a subsequent increase in the rate of ICU admission and length of stay; (iii) patients with pulmonary complications had a lower rate of penicillin and macrolide resistance; (iv) pulmonary complications were not significantly different when PCV7 serotypes were compared with non-PCV7 serotypes; (v) and COPD was a protective factor against pulmonary complications.

TABLE 8. Significant univariate and multivariate logistic regression analyses of complicated pulmonary pneumonia

	Univariate			Multivariate[a]		
Variable	OR	95% CI	p-Value	OR	95% CI	p-Value
Age >65 years	0.65	0.47–0.90	0.010	–	–	–
Pneumococcal vaccine	0.65	0.38–1.09	0.099	–	–	–
Chronic respiratory disease[b]	–	–	0.001	–	–	0.001
None	1	–	–	1	–	–
Bronchiectasis	0.92	0.53–1.58	0.76	0.84	0.47–1.49	0.55
COPD	0.37	0.23–0.59	<0.001	0.38	0.23–0.63	<0.001
Asthma	1.16	0.61–2.22	0.65	1.43	0.72–2.86	0.31
Other	0.58	0.28–1.17	0.13	0.51	0.24–1.10	0.084
Chronic liver disease	2.42	1.24–4.71	0.009	3.60	1.71–7.60	0.001
Bacteraemia	1.61	1.15–2.27	0.006	–	–	–
Creatinine >1.5 mg/dL	1.90	1.27–2.82	0.002	2.01	1.31–3.08	0.001
C-reactive protein ≥18 mg/dL	2.72	1.92–3.86	<0.001	2.77	1.91–4.00	<0.001

COPD, chronic obstructive pulmonary disease.
[a]Hosmer–Lemeshow goodness-of-fit test: p 0.57.
[b]The p-value corresponds to differences between the five groups (none, bronchiectasis, COPD, asthma, or other chronic respiratory disease). The OR and 95% CI of bronchiectasis, COPD, asthma and other chronic respiratory disease are related to cases with no chronic respiratory disease.

In the present study, we found that patients with pneumococcal pneumonia had 38% of pulmonary complications as defined. This is the first study evaluating the clinical impact of pulmonary complications in hospitalized adults with pneumococcal pneumonia. Other publications have reported these complications only erratically. For example, in a previous study in adults, empyema was reported in 2% [18], and another study reported multilobar infiltrates in 37% [19]. Our study characterized a population of pneumococcal CAP patients who developed pulmonary complications, showing that they were younger and had fewer comorbidities (especially COPD) than patients without pulmonary complications. The concept of grouping pulmonary complications together comes from paediatricians who have studied children with and without complications of pneumococcal pneumonia [20]. Indeed, two previous studies described several risk factors associated with an increased risk of pulmonary complications in children as follows: younger age, black race, low weight, and anaemia [13,20]. In our study, all of the analysed pulmonary complications clearly showed a positive association with parameters of CAP severity such as ICU admission and length of hospital stay. This finding supports our motivation to investigate prognostic factors for the development of pulmonary complications.

Patients with complicated CAP had a lower rate of COPD and a higher rate of chronic liver disease. Other differential characteristics of complicated pneumonia were a higher inflammatory response (as assessed by higher CRP levels) and a higher percentage of bacteraemia, shock, ICU admission and MV than in uncomplicated pneumonia. The length of stay was higher for patients with complicated pneumonia, but the mortality rate did not significantly differ between the two study groups (9% vs. 8%). It is probable that all of these clinical and biological characteristics will, in the future, help clinicians to identify patients who may need a higher degree of monitoring and/or ICU care [21].

In the present study, we found that the rates of resistance to penicillin and macrolide were significantly higher in patients without pulmonary complications. A reduced rate of antibiotic resistance has also been observed in previous studies on adult patients with pneumococcal bacteraemia, in recent studies of adult patients with septic shock and of children with pulmonary complications of pneumococcal pneumonia [20,22].

We were able to determine the pneumococcal serotype in 84 invasive strains. On comparison of serotype distribution in the two population groups, we found no statistically significant differences (p 0.42) in relation to pulmonary complications according to serotype group (PCV7 serotype vs. non-PCV7 serotypes); however, we found a trend for a higher rate of serotype 19A in patients with complicated pneumonia. Other studies have found that serotype 19A is more frequent among adults and children with IPD and complicated pneumococcal pneumonia [4,22]. In a landmark study, the incidence of IPD in adults was found to have decreased since the PCV7 vaccine was introduced. In contrast, the incidence of more virulent serotypes (3 and 19A) had increased in parallel [23]. A recently published study by Garcia-Vidal *et al.* [22] showed that serotype 3 was more frequent in patients with pneumococcal pneumonia presenting with shock. All of these data are crucial for the development of new vaccines. Fortunately, the new conjugate 13-valent pneumococcal vaccine includes serotypes 1, 3, and 19A, and is currently being tested in adults aged over 65 years [24].

Chronic liver disease was one of the factors associated with an increased risk of pulmonary complications in the multivariate analysis. Another study by our group has shown that chronic liver disease is a risk factor for complications and poor outcomes [25]. An elevated CRP level (≥18 mg/dL) at admission was also found to be a risk factor for the development of pulmonary complications. Chalmers *et al.* [26] found that low admission CRP levels were associated with negative predictive value for 30-day mortality, MV, inotropic support, and complicated pneumonia. In the other hand we found that eleveated creatinine (>1.5mg/dL) at atmission was another risk factor for pulmonary complications. This parameter is a marker of a bad outcome, as has been described previously [27]. In the same analysis, we found that only COPD was a protective factor against the development of pulmonary complications. Why COPD is a protective factor against pulmonary complications is difficult to explain. However, in a recent cellular study by our group [28], we observed the activation of different phenotype macrophages in CAP with and without COPD, indicating different inflammatory responses. This different type of activation induces different inflammatory responses, and may be involved in the better outcome of CAP observed in some studies when COPD presents simultaneously [28]. Similarly, Strassburg *et al.* [29] found decreased apoptosis of pulmonary neutrophils in COPD patients with CAP, indicating an increased inflammatory response to the bacterial load in these patients. COPD was also found to be a protective factor against non-responding pneumonia in another study from our group investigating factors associated with treatment failure in CAP [8].

Investigation of antibiotic treatment in our population showed a significantly higher rate of β-lactam plus fluoroquinolone treatment in patients with complicated CAP. In contrast, we observed a higher rate of fluoroquinolone monotherapy in patients with uncomplicated CAP. These

differences can probably be explained by the disease severity, which influenced clinicians to use a potent antibiotic combination for complicated CAP and monotherapy for uncomplicated CAP. In the study period, our hospital routinely followed the recommendations of the Spanish Society of Pulmonology and Thoracic Surgery for the empirical treatment of CAP [30]. Following these guidelines (β-lactam plus macrolide or quinolone as monotherapy), we found that initial antibiotic treatment was adequate in patients for whom an antibiogram was available.

The strengths of our study are as follows: (i) a large population of consecutive patients included over a period of 9 years; (ii) the application of the concept of pulmonary complications in adults for the first time in CAP, following what has been previously published for the paediatric population [14] the concept of complicated pneumonia could be debated but in our opinion it represents a CAP subpopulation that can be distinguished specifically; and (iii) the study of antibiotic resistance in most of the strains, and serotype information for the last 4 years. A limitation of the study is the lack of information about the time to the first dose of antibiotic, a variable that may potentially influence mortality. Moreover, serotyping results were limited to the years 2006–2009.

In summary, our study describes a subpopulation of hospitalized pneumococcal pneumonia patients in whom the mortality did not differ despite the higher severity of pneumonia. COPD as a comorbidity was the only protective factor against pulmonary complications. Finally, no significant differences were observed between the serotype distributions of complicated and uncomplicated pneumonia.

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Transparency Declaration

None of the authors have any conflict of interests to declare.

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